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(71) Applicant (*for all designated States except US*): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): DESMOND, Richard [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). TSCHAEN, David, M. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). McCAULEY, James, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). VARSOLONA, Richard, J. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(74) Agent: BIGLEY, Francis, P.; Merck & Co., Inc., Patent Dept., 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

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(54) Title: MORPHOLOGICAL FORMS OF (+)-N-[1'-(6-CYANO-1,2,3,4-TETRAHYDRO-2-NAPHTHALENYL)-3,4-DIHYDRO-4-HYDROXYSPIRO[2H-1-BENZOPYRAN-2,4'-PIPERIDIN]YL]METHANESULFONAMIDE HYDROCHLORIDE

(57) Abstract

This invention relates to different morphological forms of (+)-N-[1'-(6-cyano-1,2,3,4-tetrahydro-2-naphthalenyl)-3,4-dihydro-4-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]yl]methanesulfonamide hydrochloride. These forms are prepared by selective crystallization or precipitation. In addition, this invention relates to the processes for the preparation of each of these forms.

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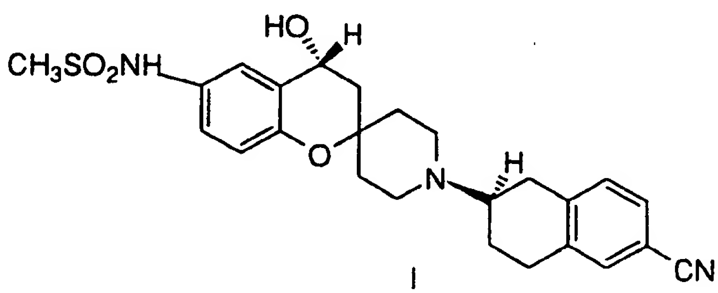
TITLE OF THE INVENTION

MORPHOLOGICAL FORMS OF (+)-N-[1'-(6-CYANO-1,2,3,4-TETRAHYDRO-2NAPTHALENYL)-3,4-DIHYDRO-4-HYDROXY-SPIRO[2H-1-BENZOPYRAN-2,4'-PIPERIDIN]YL]METHANE-SULFONAMIDE HYDROCHLORIDE

BACKGROUND OF THE INVENTION

This invention relates to different morphological forms of (+)-N-[1'-(6-Cyano-1,2,3,4-tetrahydro-2napthalenyl)-3,4-dihydro-4-hydroxyspiro-[2H-1-benzopyran-2,4'-piperidin]yl]methanesulfonamide hydrochloride, herein after referred to as COMPOUND I and the processes for the preparation of these morphologically different forms.

COMPOUND I is an antiarrhythmic agent whose structure is



I

Research studies directed at determining various means to produce solid COMPOUND I have been undertaken. The solid product of such studies was analyzed by differential scanning calorimeter (DSC), infrared spectroscopy, x-ray powder diffraction (XRPD) and thermogravimetry and it has been determined that COMPOUND I has at least nine morphological forms. These morphological forms will be referred to hereinafter as Form "A", Form "B", Form "Ca", Form "Cb", Form "D", Form "E", Form "G", Form "H" and Form "J".

Each of these morphological forms are independently useful, as described below, because of their individual, unique properties.

The morphological form of a pharmaceutical compound is of interest to those involved in the development of a suitable dosage form since if the morphological form is not held constant during clinical and stability studies, the exact dosage used or measured may not be comparable from one lot to the next. Once a pharmaceutical compound is produced for sale, it is important to recognize the morphological form delivered in each dosage form to assure that the production process use the same form and the same amount of drug is included in each dosage. Therefore, it is imperative to assure that either a single morphological form or some known combination of morphological forms is present at all times.

Differences between morphological forms have reportedly been shown to result in surprising differences in the bioavailability of a particular compound. For example in the case of mebendasole [Janssen Pharmaceutica: Clin. Res. Reports No. R 17635/36 (1973)], differences in bioavailability between the morphological forms have been reported.

The object of this invention is to determine the morphological forms of COMPOUND I. An additional object of this invention is to determine which methods can be use to prepare these morphological forms.

SUMMARY OF THE INVENTION

The instant invention is concerned with nine novel morphological forms of COMPOUND I. COMPOUND I Form "A" is the dihydrate form of the molecule. COMPOUND I Form "B" is a monohydrate. COMPOUND I Form "Ca" is the anhydrous form of COMPOUND I Form "A". COMPOUND I Form "Cb" is the anhydrous form of COMPOUND I Form "B". COMPOUND I Form "D" is a dihydrate. COMPOUND I Form "E" is a mono-isopropanol solvate. COMPOUND I Form "G" is a mono-ethanol solvate. COMPOUND I Form "H" is a mono-methanol solvate. COMPOUND I Form "J" is an anhydrous form of the compound. In addition, the instant invention is also concerned with the method of preparing each of these novel morphological forms.

DETAILED DESCRIPTION OF THE INVENTION

The conversion of COMPOUND I free base to COMPOUND I was determined to be complicated by several factors. The most prominent concern with this seemingly trivial transformation is the existence of multiple morphological forms. Each of these morphological forms has unique properties which can be exploited during manufacturing or in the design of a dosage form. Therefore, each is of independent interest.

COMPOUND I can be synthesized using the procedure described in United States Patent 5,206,240, which issued to Baldwin et al. on April 27, 1993, which is hereby incorporated by reference. This synthesis is reproduced herein for convenience.

(+)-N-[1'-(6-Cyano-1,2,3,4-tetrahydro-2-napthalenyl)-3,4-dihydro-4-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]yl]methanesulfonamide hydrochloride was prepared as follows, (+)-N-[1'-(6-Cyano-1,2,3,4-tetrahydro-2-napthalenyl)-3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]yl]methanesulfonamide (581 mg, 1.25 mmol) was dissolved with warming in methylene chloride (20 ml) and cooled to -20°C. A solution of (S)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2,c][1,3,2]-oxazaborole-borane complex (400 mg, 1.38 mmol) in methylene chloride (4 ml) was added dropwise and the mixture was stirred under argon at -20 to -15°C for 1 h, then at ambient temperature for 30 min. Methanol (20 ml) was added, followed after 10 min. by HCl-H_2O (1M, 10 ml). The mixture was stirred for 1 h., diluted with aqueous sodium hydrogen carbonate (Saturated, 20 ml) and extracted with methylene chloride (3 x 20 ml). The combined organic fractions were dried (Na_2SO_4) and evaporated under reduced pressure to give a white foam (981 mg). This was dissolved in methylene chloride (25 ml) and cooled in ice. Four portions of acetic anhydride (132 ml, 142 mg, 1.4 mmol) were added at hourly intervals. After 4 h. at 0°C, the mixture was stirred at ambient temperature for a further 20 h. Methanol (10 ml) and aqueous sodium hydrogen carbonate (Saturated,

10 ml) were added and the mixture was stirred vigorously for 1 h. Aqueous sodium hydrogen carbonate (Saturated, 20 ml) was added and the mixture was extracted with methylene chloride (3 x 20 ml). The combined organic fractions were dried (Na_2SO_4) and evaporated under reduced pressure to give a white foam (1.05 g). The residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/-MeOH/NH_3-H_2O (94:6:0.6 increasing to 90:10:1), re-chromatographing impure fractions. Pure fractions were evaporated under reduced pressure, redissolved in CH_2Cl_2 (20 ml), filtered through anhydrous Na_2SO_4 and evaporated under reduced pressure to give a white foam (369 mg, 63%). The residue was dissolved in ethanol (4 ml) and HCl-EtOH (6M, 0.5 ml) was added dropwise with stirring. The mixture was stirred at ambient temperature for 1 h., then refrigerated over night. The solid was collected by filtration under argon, then dried in vacuo at ambient temperature for 48 h. and at 35°C for 24 h to give the hydrochloride as a white solid (321 mg), m.p. 211-213°C, $[\alpha]D$ +30.5° (c = 0.102, MeOH).

HPLC analysis [Ultron ES OVM column; 0.3% n-propanol/ammonium foramate-water (12 g/l)] showed this to be the faster eluting diastereoisomer.

Elementary analysis

Calc'd for $C_{25}H_{30}ClN_3O_4S$:

C 59.57; H 6.00; N 8.34%.

Found: C 59.45; H 5.76; N 8.40%.

The compounds of Table LVIII were prepared according to the method described in Example 556 by reducing the appropriate ketone with (R)- or (S)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo-[1,2,c][1,3,2]oxazaborole-borane complex as indicated.

The preparation of N-[1'-(6-cyano-1,2,3,4-tetrahydro-2-naphthalenyl)-3,4-dihydro-4-oxospiro-[2H-1-benzopyran-2,4'-piperidin]-6-yl]methane-sulfonamide, its monohydrochloride and separation into its enantiomers was accomplished as follows:

<u>Step 1</u>: <u>Preparation of 6-Bromo-2-tetralone</u>

A single neck 3 liter round bottom flask under an Ar atmosphere was charged with 4-bromo-phenyl acetic acid (250.0 g, 1.15 m), methylene chloride (1.5 L), and dimethylformamide (0.5 mL). This magnetically stirred solution was cooled to 0°C and treated dropwise with oxalyl chloride (156 mL, 1.74 m). The reaction was allowed to reach room temperature and stirred 16 hrs. The reaction was concentrated on a rotary evaporator to approximately 1 L of volume. A separate dry 5 liter 3 neck round bottom flask under Ar, fitted with gas inlet tube, overhead stirrer, and digital thermometer was charged with methylene chloride (1.5 L) and $AlCl_3$ (312.0 g, 2.34 m). This suspension was cooled to 0°C and stirred while the above solution of acid chloride was added to it slowly via cannula. When the addition was complete, ethylene gas was introduced for 1-2 hrs to the vigorously stirred suspension while maintaining the internal temperature at 15°C. Upon completion by HPLC, the reaction was warmed to room temperature and stirred for 0.5 hrs. The mixture was recooled to 0°C and cautiously quenched slowly with water (1.5L). The layers were separated, and the aqueous one washed with 500 mL of methylene chloride. The organic portion was washed with 2N aqueous HCl (2 X 800 mL), brine (400 mL), and saturated aqueous $NaHCO_3$ (2 X 800 mL). Each aqueous extract was washed with the same 500 mL methylene chloride extract from above. The methylene chloride extracts were combined, dried (Na_2SO_4), filtered, and concentrated to approximately 500 mL of volume. This was then added to 5.0 L of hexane warmed to 50°C. The methylene chloride was distilled off and the hot solution decanted from an insoluble brown tar. The solution was allowed to cool to 25°C and placed in the freezer overnight. The precipitate was collected and washed with hexane (200 mL), and dried <u>in vacuo</u> to give 229.0 g of the COMPOUND Is a pale yellow solid (88%).

<u>Step 2</u>: <u>Preparation of (+)-1,4-dioxa-8-(6'-bromo-1',2',3',4'-tetrahydronaphth-2'-yl)-8-azaspiro[4.5]decane</u>

A 3 L round bottom flask fitted with an argon inlet, and Deak-Stark apparatus was charged with a solution of 6-bromo-2-tetralone (100.0 g, 445 mmol) in toluene (2.0 L). Para-toluenesulfonic acid (0.50 g) and 1,4-dioxa-8-azaspiro[4,5]-decane (81.5 g, 489 mmol) were added and the stirred mixture heated to reflux and the water removed (4.5 hrs). The mixture was cooled, and concentrated to an oil <u>in vacuo</u>. The oil was dissolved in anhydrous tetrahydrofuran (1.5 L) and cooled to 0°C under argon. Dry HCl gas was introduced (at below 5°C) and a solid precipitate formed. Sodium cyanoborohydride (36.3 g, 578 mmol) was added in four portions. The reaction was allowed to warm gradually to room temperature and stirred 16 hrs. This was quenched with 1N aqueous sodium hydroxide (500 mL) and stirred for 0.5 hr (pH=13.5). The mixture was concentrated on a rotary evaporator to remove THF, and diluted with 1N NaOH (1.1 L) and diethyl ether (1.5 L). This mixture was stirred 15 min and the layers were separated and the aqueous layer was washed with diethyl ether (2 X 200 mL). The organic layers were combined, washed with water (2 X 500 mL) and saturated aqueous NaC1 (2 X 250 mL) and then with 1N HC1 (1 X 1.0 L, 2 X 500 mL). The acid extracts were combined, stirred with methylene chloride (1.0L), and basified with 40% aq. NaOH (pH=10). The layers were separated, and the aqueous extracted with methylene chloride (500 mL). The methylene chloride extracts were combined, dried (Na_2SO_4), and concentrated to an oil. The oil was flushed with toluene (2 X 400 mL) and dried <u>in vacuo</u> to give the title COMPOUND Is a solid on standing (128.8 g, 87%) which was greater than 98% pure by HPLC and used in the next step without purification. **Note:** The amount of of excess HCl gas present (pH=3-4, THF suspension on wet pH paper) critically determines the yield free amine. Additional HC1 may be added during the introduction of the cyano borohydride. In runs in which the pH was not adjusted properly the yield was reduced to 50%; the balance being a borane complex which was isolated from the ether layers. This borane complex could

be quantitatively converted to the free amino by heating in 40% aq NaOH/ethylene glycol (1:1) at 100°C.

Step 3(a): Preparation of Phenyl cyanate

The title compound was prepared by a modification of the procedure described in Organic Syntheses, 61, 35 (1983). A 3-necked, 2 L R.B. flask, equipped with a 500 ml pressure equalized dropping funnel, a mechanical stirrer and a thermometer, was charged with water and cooled in an ice-salt bath. Cyanogen bromide (189.1 g, 1.78 mol) was added and the mixture was stirred for 5 min. Phenol (160.0 g., 1.7 mol) in carbon tetrachloride (535 ml) was added in one portion. The mixture was stirred vigorously while triethylamine (236.9 ml, 172.0 g, 1.7 mol) was added dropwise at a rate such that the reaction temperature did not exceed 5°C (total addition time = 45 min.). The mixture was stirred for a further 15 min. then transferred to a 2 L separatory funnel. The organic layer was separated and the aqueous layer was extracted with carbon tetrachloride (2 X 90 ml). The combined organic layers were washed with water (3 X 90 ml) then dried by stirring with phosphorus pentoxide (10 g) for 15 min. The mixture was filtered and the solvent was evaporated under reduced pressure (water aspirator) at 20°C to give a yellow oil. Polyphosphate ester (Y. Kanaoka, et al., Chem. Pharm. Bull., 13, 1065-1072 (1965)) (0.2 ml) was added and the mixture was distilled under reduced pressure through a 15 cm vigreux column to give phenyl cyanate (165.8 g, 82%) as a colorless oil, b.p. 79-82°C (16 mmHg)[1]. The product was stored under nitrogen at -10°C (freezes).
1H NMR (300 MHz, $CDCl_3$) δ: 7.49-7.30 (5H, m).

Step 3 (b): Preparation of(+)-1,4-Dioxa-8-(6'-cyano-1',2',3',4'-tetrahydronapath-2yl)-8-azaspiro[4.5]decane

(+)-1,4-Dioxa-8-(6'-bromo-1',2',3',4-tetrahydronaphth-2-yl)-8-azaspiro[4.5]decane (70.4 g, 0.2 mol) under nitrogen in a 1 L R.B. flask was dissolved in anhydrous THF (600 ml, distilled from Na/benzophenone) and cooled to -75°C. Phenyl cyanate (26.06 ml, 28.5 g, 0.24

mol) dissolved in anhydrous THF (400 ml) under nitrogen in a 2 L R.B. flask equipped with a digital thermometer was cooled to -75°C. n-Butyl lithium (1.6M in hexane, 137.5 mL, 0.22 mmol) was added over 5 min. to the bromide solution. Further n-butyl lithium (12.5 mL, 0.02 mmol) was added to the phenyl cyanate solution. After 5 min., the lithiated bromide solution was added over 5 min., via cannual, to the phenyl cyanate solution (reaction temperature rises to -35°C). The mixture was stirred and cooled to -75°C for 30 min. then the cooling bath was removed and HC1-H_2O (1M, 200 mL) was added with vigorous stirring. The mixture was warmed to room temperature, diluted with HC1-H_2O (1M, 1800 mL) and washed with ether (2 X 1000 mL.). Methylene chloride (1000 mL) was added and the mixture was stirred and cooled in ice during the addition of aqueous sodium hydroxide 10 M, 180 mL). The layers were separated, and the aqueous layer was extracted with methylene chloride (500 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to give crude (+) 1,4-dioxa-8-(6'-cyano-1',2',3',4'-tetrahydro-naphth-2'yl)-8-azaspiro[4.5]decane as a tan solid (56.2 g). Crude (+)1,4-dioxa-8-(6'-cyano-1',2',3',4'-tetrahydro-naphth-2'yl)-8-azaspiro-[4.5]-decane in three batches (56.4 g, 56.2 g, 27.7 g; total 140.3 g) were separately dissolved in refluxing methyl-cyclo-hexane (1000 mL each) and combined by decanting into a 5 L, 4-necked flask equipped with a mechanical stirrer, thermometer, reflux condenser and a stopper. The mixture was heated to reflux (clear solution formed), then allowed to cool with stirring to room temperature, then to 5°C. The mixture was stored at -15°C for 15 hr. The solid was collected by filtration, washed with cold methylcyclohexane (2 X 150 ml) and dried in vacuo at room temperature to give the spirodecane as a pale yellow solid (121.3 g), .m.p. 136-138°C. Purity = 99.3%

Step 4: Resolution of 1,4-dioxa-8-(6'-cyano-1'2',3'4'-tetrahydronaphth-2'-yl)-8-azaspiro[4.5]decane

A 12 L round bottom flask fitted with a reflux condenser, digital thermometer, and overhead stirrer was charged with absolute

ethanol (10.6 L) and 1,4-dioxa-8-(6'-cyano-1',2',3',4'-tetrahydronaphth-2'yl)-8-azaspiro[4.5]decane 120.0 g, 402 mmol). The mixture was warmed to 65°C to give a clear solution, and 97% di-p-toluoyl-L-tartaric acid monohydrate (167.7 g, 402 mmol) was added. The resulting clear solution was seeded with this salt and allowed to cool to room temperature with stirring overnight. The precipitate was collected by filtration and washed with absolute ethanol (600 mL). The solid was dried in vacuo to a solid and converted to free base in a stirred mixture of ethyl acetate (2.0 L) and saturated aqueous $NaHCO_3$ (3.0L). The layers were separated, and the aqueous one washed with ethyl acetate (2 X 500 mL). The organic layers were combined, washed with brine (2 X 200 mL), dried (Na_2SO_4), and concentrated to 69.4 g of a solid (59% yield). The solid free base (69.4 g, 233 mmol) was dissolved in absolute ethanol (4.25 L) at 60°C and 97% di-p-toluoyl-D-tartaric acid (92.64 g, 233 mmol) was added. The resulting clear solution was seeded with a sample of this salt and allowed to cool to room temperature overnight. The precipitate which formed was collected, washed with absolute ethanol (800 mL), and dried in vacuo at 40°C to give 122.5 g (44.5%). This + D salt was completely dissolved in absolute ethanol (8.0L) at reflux and concentrated to approximately 7.0 L of volume by distillation at 1 atmosphere. The solution was seeded and cooled to room temperature overnight. The solid was collected, washed with absolute ethanol (800 mL) dried in vacuo to give 100.9 g [α]D=+104.7° (c= 1.0 pyridine)) (36.7%). This salt was dissolved in hot absolute ethanol (8.3L), concentrated at 1 atmosphere to 3.1 L of total volume, seeded and cooled to room temperature overnight. This solid was collected, washed with absolute ethanol (900 mL) and dried in vacuo to give 89.7 g [α]D=105.4° (c=1.0 pyridine)) (32.6%). A further crystallization from 7.0 L hot ethanol concentrated to 2.9 L volume gave 74.3 g ([α]D=+105.4° (c=1.0 pyridine)) (32.6%). A further recrystallization from 7.0 L hot ethanol concentrated to 2.9 L volume gave 74.3 g [α]D=104.9° (c=1.0 pyridine)) (27% yield). The free base was obtained by treating a stirred mixture of saturated aq. $NaHCO_3$ (250 mL) and methylene chloride (250 mL) with 1,4-dioxa-8-

(6'-cyano 1',2',3',4'-tetrahydronaphth-2'yl)-8-azaspiro]4.5]decane di-p-toluoyl-D-tartaric acid salt (10.0 g, 33.5 mmol). After 15 min the layers were separated, the aqueous washed with methylene chloride (100 mL), and the combined organics washed with saturated aq. $NaHCO_3$ (100 mL), dried Na_2SO_4) and concentrated to give 4.30 g (99%) of a solid. A sample of free base was analyzed by chiral shift reagent proton NMR to be 99.8% pure (+) enantiomer.

Step 5: Preparation of N-(6'-Cyano-1',2',3',4'-tetrahydronaphth-2'-yl)piperidin-4-one

A solution of (+)-1,4-dioxa-8-(6'-cyano-1',2',3',4'-tetrahydronaphth-2'yl)-8-azaspiro[4.5]-decane (10.0 g, 33.5 mmol) was dissolved in 1N HC1 (100 mL). This was stirred and heated to 100°C under an argon atmosphere for 1.5 hrs. The solution was cooled in an ice bath to 25°C and methylene chloride added (200 mL). The mixture was stirred and basified to pH=9.0 with saturated aqueous sodium carbonate. The organic layer was separated and the aqueous extracted with methylene chloride (2X 50 mL). The combined organic extract was dried (Na_2SO_4), and concentrated to a foam to give 7.5 g (99%) of N-(6'-cyano-1',2',3',4'-tetrahydronaphth-2'-yl)-piperdin-4-one (98% by HPLC).

Step 6: Methanesulfonamide, N-[1'-(6-cyano-1,2,3,4-tetrahydro-2-naphthalenyl)-3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-monohydrochloride

A solution of 2-hydroxy-5-methanesulfonamido-acetophenone (26.98 g, 117.7 mmol), and pyrrolidine (9.8 mL, 117.7 mmol) in methanol (480 mL) was stirred at 25°C for 10 min. (+)-N-(6'-Cyano-1',2'3',4'-tetrahydronaphth-2'-yl)-piperidin-4-one (20.0 g, 78.4 mmol) was added in one portion and the mixture stirred for 24 hrs at 25°C. The reaction was concentrated to an oil in vacuo and flash chromatographed (silica gel, ethyl acetate) to afford the product in appropriate fractions which were combined and concentrated to a foam. This was crystallized from isopropyl alcohol (525 mL) to give a solid

which was collected by filtration, washed with IPA (50 mL) and dried in vacuo (30.8 g). This was dissolved in ethyl acetate (1.5L) and treated with 1.3N HCl in IPA (55 mL). The precipitate was stirred 20 hrs, filtered and dried in vacuo (60°C. 0.1 torr) to give 32.3 g (84%) of (+) Methanesulfonamide, N-[1'-(6-cyano-1,2,3,4-tetrahydro-2-naphthalenyl)-3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, [α]D = +40.7 (c=0.17, MeOH).

COMPOUND I Form "A" is one of the preferred morphological forms of this compound. COMPOUND I Form "A is a dihydrate which is stable as an isolated solid at ambient humidities. Ambient humidities is defined as humidity within the range of about 15% to about 95% relative humidity. COMPOUND I Form "A" can be prepared from COMPOUND I free base as follows by dissolving the free base in acetone and warming to about 45°C. Aqueous hydrochloric acid is then added as the acetone is distilled off. The precipitate is COMPOUND I Form "A". It is filtered and dried at room temperature. Form "A" is useful in the production since it is not as hygroscopic as some of the other morphologic forms and therefore is easy to weigh.

COMPOUND I Form "A" can be converted to it's corresponding anhydrous form, Form "Ca" under very dry conditions. By "very dry" conditions is meant conditions where the relative humidity is less than about 15%. Rehydration from COMPOUND I Form "Ca" to COMPOUND I Form "A" is possible. This rehydration can be achieved by mixing COMPOUND I Form "Ca" as a slurry in water at elevate temperatures, that is above about 40°C. Form "Ca", being practically anhydrous, provides a very useful form for long term storage of COMPOUND I at low humidity (less than 10% relative humidity) reducing the chance of water catalyzed decomposition products forming during storage.

However, when COMPOUND I Form "A" is mixed as a slurry in water at temperatures below about 40°C, COMPOUND I Form "D" is produced. Seeding with COMPOUND I Form "D" will

assure the production of this morphological form, however, seeding is not essential.

If COMPOUND I Form "D" is dried with heat, or the compound is exposed to ambient relative humidities between about 10% to about 58%, the monohydrate, COMPOUND I Form "B" is produced. COMPOUND I Form "B" can be dried to the anhydrous COMPOUND I Form "Cb" which rehydrates to COMPOUND I Form "B" under a relative humidity which is greater than about 10% but less than about 58%. COMPOUND I Form "Cb", although only stable at low humidity, is the fastest dissolving of the polymorphic forms found. This form is particularly useful when a rapid dissolving form of COMPOUND I is needed during production of solutions or for use in wet granulations. COMPOUND I Form "D", on the other hand, is the slowest form to dissolve. COMPOUND I Form "D" would be particularly useful if a slower dissolving dosage form was desired.

COMPOUND I Forms "E", "G" and "H" are the isopropanol, ethanol and methanol solvates, respectfully. These are particularly useful when wet granulations of COMPOUND I are to be prepared as these are already assoicated with the particular alocohol used in the wet granulation process.

COMPOUND I Form "J" is prepared by dissolving COMPOUND I free base in acetone or methylethylketone and adding aqueous hydrochloric acid. COMPOUND I Form "J" has been shown to be faster dissolving than COMPOUND I Form "A". Therefore, it may offer a benefit in terms of <u>in vitro</u> dissolution or <u>in vivo</u> bioavailability. Compound I form "J" is also nonhygroscopic at room temperature when the relative humidity is as high as 90%. Therefore, it offers the advantage of being easy to weigh during manufacturing.

EXAMPLES

EXAMPLE 1

COMPOUND I Form "A"

COMPOUND I Form "A" was prepared by dissolving 1 g of COMPOUND I free base per 1.5 mL of acetone. The solution is warmed to about 45°C and aqueous HCl (3.0 M) is added. The resulting mixture is stirred to produce a clear solution. Water (7 mL/ g of COMPOUND I free base) is added while the acetone is distilled off. The crystalline COMPOUND I precipitates from the solution during the distillation.

It has been found that heating the solution above 50°C can result in some racemization of the COMPOUND I benzylic alcohol center. It has also been shown that the particle size of the resulting crystals is dependent upon the rate at which acetone is distilled. Faster rates of evaporation lead to smaller particles. COMPOUND I Form "A" is characterized by an x-ray diffraction pattern with reflections at 16.6, 8.2, 6.2, 5.5, 5.3, 4.6, 4.4, 4.2, 4.1 and 3.7 Å; characteristic peaks observed by diffuse reflectance infrared spectroscopy at 3350, 3114, 2914, 2854, 2669, 2626, 2584, 2556 and 2224 cm^{-1}; and a differential scanning calorimeter curve, at a heating rate of 10°C/min in an open cup and under ambient air, which exhibits low temperature water loss endotherm with an extrapolated onset temperature of 60°C, peak temperature of 80°C and an associated heat of about 160 Joules/gm and a melting-decomposition endotherm with an extrapolated onset temperature of about 205°C, peak temperature of 215°C and an associated heat of about 25 Joules/gm. The thermogravimetry curve shows a single step wise weight loss of about 6.4% from room temperature to about 150°C. The theoretical weight loss for a dihydrate of COMPOUND I is 6.66%.

EXAMPLE 2

COMPOUND I Form "B"

COMPOUND I Form "B" has been prepared by heating COMPOUND I Form "D" at about 75°, producing a mono-hydrate of COMPOUND I.

COMPOUND I Form "B" is characterized by an x-ray powder diffraction pattern with reflections at 15.3, 727, 5.4, 4.9, 4.6, 4.5, 4.4, 4.3, 4.1, 4.0, 3.9 and 3.8 Å; characteristic peaks observed by diffuse reflectance infrared spectroscopy at 3580, 3486, 3411, 3110, 3039, 2929, 2856, 2671, 2585, 2557, 2430 and 2225 cm^{-1}; a differential scanning calorimeter curve, at a heating rate of 10°C/min in an open cup and under ambient air, which exhibits low temperature water loss endotherm with an extrapolated onset temperature of about 110°C, peak temperature of 125°C and an associate heat of about 85 Joules/gm plus a melting-decomposition endotherm with an extrapolated onset temperature of about 203°C, peak temperature of 212°C and an associated heat of about 20 Joules/gm; and a thermogravimetric curve having a single step wise weight loss of about 3.4% from room temperature to about 150°C. Theoretical weight loss for a monohydrate of COMPOUND I is 3.33%.

EXAMPLE 3

COMPOUND I Form "Ca"

COMPOUND I Form "Ca" has been made by heating COMPOUND I Form "A' at about 100° until it is dry.

COMPOUND I Form "Ca" is characterized by x-ray powder diffraction pattern with reflections at 16.8, 8.8, 8.3, 6.5, 5.7, 5.6, 4.9, 4.4, 4.2, 4.1 and 3.7 Å.

EXAMPLE 4

COMPOUND I Form "Cb"

COMPOUND I Form "Cb" has been prepared by heating COMPOUND I Form "D" or Form "B" at about 125°C until it is dry.

COMPOUND I Form "Cb" is characterized by an x-ray diffraction pattern with reflections at 10.0, 8.3, 6.5, 5.5, 5.2, 4.8, 4.4, 4.1, 4.0 and 3.8 Å.

EXAMPLE 5

COMPOUND I Form "D"

COMPOUND I Form "D" has been prepared by dissolving about 40 mg of COMPOUND I free base in one mL of isopropanol/water (1:1 v/v) at room temperature. The solution was cooled to between 0 and 5°C and one molar equivalent to the COMPOUND I free base, of cold (0 - 5°C) aqueous hydrochloric acid (6N) was added with stirring over two hours. The resulting slurry was filtered and the solid phase was collected and air dried at room temperature.

COMPOUND I Form "D is characterized by an x-ray diffraction pattern with reflections at 9.5, 8.3, 6.7, 5.5, 4.9, 4.5, 4.4, 4.1, 4.0 and 3.6 Å; characteristic peaks observed by diffuse reflectance infrared spectroscopy at 3380, 3350, 3239, 3120, 2925, 2854, 2696, 2587, 2446, 2288 and 2225 cm^{-1}; and a differential scanning calorimetry curve, at a heating rate of 10°C/min in an open cup and under ambient air, which exhibits two low temperature water loss endotherms, the first low temperature water loss endotherm having an extrapolated onset temperature of about 45°C with a peak temperature of 56°C and an associated heat of about 85 Joules/gm, the second low temperature water loss endotherm having an extrapolated onset temperature of about 110°C, with a peak temperature of 125°C and an associated heat of about 85 Joules/gm, and a melting-decomposition endotherm, having an extrapolated onset temperature of about 203°C

and a peak temperature of 212°C and an associated heat of about 20 Joules/gm. The thermogravimetry curve shows two step wise weight loss of about 3.3% each, for a total of 6.6%, from room temperature to about 150°C. The theoretical weight loss for a dihydrate of COMPOUND I is 6.66%.

EXAMPLE 6

COMPOUND I Form "E"

COMPOUND I Form "E" was prepared by slurring COMPOUND I in isopropanol at a concentration of 100 mg of COMPOUND I/ mL of isopropanol. The resulting slurry was stirred overnight and the solid phase was collected and dried at room temperature.

Alternately,.COMPOUND I Form "E" was prepared by dissolving COMPOUND I in isopropanol and reducing the volume of isopropanol with a stream of air to induce precipitation. The precipitate was collected and dried at room temperature.

COMPOUND I, Form "E" is characterized by an x-ray diffraction pattern with reflections at 15.4, 9.4, 6.8, 6.1, 5.7, 5.2, 4.7, 4.4, 4.1, 3.6 and 3.3 Å and a thermogravimetry curve having a single step wise weight loss of about 11.1% from room temperature to about 150°C. Theoretical weight loss for a mono-isopropanol solvate of COMPOUND I is 11.9%.

EXAMPLE 7

COMPOUND I Form "G"

COMPOUND I Form "G" was prepared by making a slurry of COMPOUND I in ethanol and stirring overnight. The resulting solid phase was collected and dried. Alternatively, COMPOUND I can be dissolved in ethanol or in up to 10 volume percent of water in ethanol (100 mg of COMPOUND I/ mL of solvent). The resulting solution was concentrated with a stream of air until

precipitation occurred. The solid phase was collected and dried at room temperature.

COMPOUND I, Form "G" is characterized by an x-ray diffraction pattern with reflections at 9.2, 8.1, 6.6, 5.1, 4.9, 4.6, 4.5, 4.3, 4.0, 3.9 and 3.5 Å and a thermogravimetry curve having a single step wise weight loss of about 8.1% from room temperature to about 150°C. Theoretical weight loss for a mono-ethanol solvate of COMPOUND I is 8.36%.

EXAMPLE 8

COMPOUND I Form "H"

COMPOUND I Form "H" has been prepared by preparing a slurry of COMPOUND I in methanol or in up to 70 volume percent water in methanol (100 mg COMPOUND I/mL of solvent) and stirring overnight. The solid phase was collected and dried at room temperature. Alternatively, COMPOUND I Form "H" has been prepared by dissolving COMPOUND I in methanol or methanol containing up to 70 volume percent water and reducing the volume with a stream of air until precipitation occurs. The solid phase was then collected and dried at room temperature.

COMPOUND I Form "H" is characterized by an x-ray diffraction pattern with reflections at 9.2, 8.1, 6.6, 5.1, 4.9, 4.6, 4.5, 4.3, 4.0 and 3.9 Å and a thermogravimetry curve having a single step wise weight loss of about 5.7% from room temperature to about 150°C. Theoretical weight loss for a mono-ethanol solvate of COMPOUND I is 5.97%.

EXAMPLE 9

COMPOUND I Form "J"

COMPOUND I Form "J" has been prepared by dissolving COMPOUND I free base in methylethylketone or acetone(about 100 mg of COMPOUND I free base/ mL of solvent) at room temperature and

adding a molar equivalent (to the COMPOUND I free base) amount of aqueous hydrochloric acid (6N) over two hours. The resulting slurry was filtered and the solid phase collected and air dried at room temperature.

COMPOUND I Form "J" is characterized by an x-ray diffraction pattern with reflections at 9.5, 5.7, 5.6, 5.4, 4.8, 4.6, 4.1, 3.9, and 3.6 Å; characteristic peaks observed by diffuse reflectance infrared spectroscopy at 3507, 3257, 3040, 3033, 3020, 2943, 2931, 2868, 2632, 2543, 2520 and 2246 cm^{-1}; a differential scanning calorimetry curve, at a heating rate of 10°C/min in an open cup and under a nitrogen stream having a single melting-decomposition endotherm with an extrapolated onset temperature of about 247°C , a peak temperature of 264°C and an associated heat of about 145 Joules/gm, a thermo-gravimetric curve having essentially no weight loss from room temperature to about 200°C.

WHAT IS CLAIMED IS:

1. A morphological form of COMPOUND I, Form "A" which is characterized by an x-ray diffraction pattern with reflections at 16.6, 8.2, 6.2, 5.5, 5.3, 4.6, 4.4, 4.2, 4.1 and 3.7 Å; characteristic peaks observed by diffuse reflectance infrared spectroscopy at 3350, 3114, 2914, 2854, 2669, 2626, 2584, 2556 and 2224 cm^{-1}; and a differential scanning calorimeter curve, at a heating rate of 10°C/min in an open cup and under ambient air, which exhibits a low temperature water loss endotherm with an extrapolated onset temperature of 60°C, peak temperature of 80°C and an associated heat of about 160 Joules/gm and a melting-decomposition endotherm with an extrapolated onset temperature of about 20°C, peak temperature of 215°C and an associated heat of about 25 Joules/gm.

2. A morphological form of COMPOUND I, Form "B" which is characterized by an x-ray powder diffraction pattern with reflections at 15.3, 727, 5.4, 4.9, 4.6, 4.5, 4.4, 4.3, 4.1, 4.0, 3.9 and 3.8 Å; characteristic peaks observed by diffuse reflectance infrared spectroscopy at 3580, 3486, 3411, 3110, 3039, 2929, 2856, 2671, 2585, 2557, 2430 and 2225 cm^{-1}; a differential scanning calorimeter curve, at a heating rate of 10°C/min in an open cup and under ambient air, which exhibits low temperature water loss endotherm with an extrapolated onset temperature of about 110°C, peak temperature of 125°C and an associate heat of about 85 Joules/gm plus a melting-decomposition endotherm with an extrapolated onset temperature of about 20°C, peak temperature of 21°C and an associated heat of about 20 Joules/gm; and a thermogravimetric curve having a single step wise weight loss of about 3.4% from room temperature to about 15°C.

3. A morphological form of COMPOUND I, Form "CA" is characterized by x-ray powder diffraction pattern with reflections at 16.8, 8.8, 8.3, 6.5, 5.7, 5.6, 4.9, 4.4, 4.2, 4.1 and 3.7 Å.

12. A method of making COMPOUND I Form "Ca" comprising the step of heating COMPOUND I Form "A' at about 100° until it is dry.

13. A method of making COMPOUND I Form "Cb" comprising the step of heating COMPOUND I Form "D" or Form "B" at about 125°C until it is dry.

14. A method of making COMPOUND I Form "D" comprising the steps of:

(a) dissolving COMPOUND I free base in a mixture of isopropanol and water (1:1 v/v);
(b) cooling to between 0 and 5°C;
(c) slowly adding, with stirring, a molar equivalent, based on the amount of COMPOUND I free base in solution, of aqueous hydrochloric acid which has been prechilled to 0 to 5°C to produce a slurry;
(d) filtering the solid phase; and
(e) air drying the solid phase.

15. The method of Claim 14, wherein the hydrochloric acid is 6 N.

16. The method of Claim 15, wherein the hydrochloric acid is added over two hours.

17. A method of making COMPOUND I Form "E" comprising the steps of:

(a) dissolving COMPOUND I in isopropanol;
(b) reducing the volume of isopropanol with a stream of air, until precipitation begins;
(c) filtering the precipitate; and
(d) drying the precipitate at room temperature.

18. The method of Claim 16, wherein the isopropanol contains up to fifteen volumes percent water.

19. A method of making COMPOUND I Form "G", comprising the steps of:
   (a) dissolving COMPOUND I in ethanol;
   (b) reducing the volume of the ethanol with a stream of air, until precipitation begins;
   (c) filtering the precipitate; and
   (d) drying the precipitate at room temperature.

20. The method of Claim 19, wherein the ethanol contains up to ten volume percent of water.

21. A method of making COMPOUND I Form "H", comprising the steps of:
   (a) dissolving COMPOUND I is methanol;
   (b) reducing the volume of the methanol with a steam of air, until precipitation begins;
   (c) filtering the precipitate; and
   (d) drying the precipitate at room temperature.

22. The method of Claim 21, wherein the methanol contains up to 70 volume percent of water.

23. A method of making COMPOUND I Form "J", comprising the steps of:
   (a) dissolving COMPOUND I free base in methylethylketone at room temperature;
   (b) slowly adding a molar equivalent, based on the amount of COMPOUND I free base in solution, of aqueous hydrochloric acid with stirring to produce a slurry;
   (c) filtering the slurry and collecting the solid material; and
   (d) air drying the solid material at room temperature.

24. The method of Claim 23, wherein acetone is substituted for methylethylketone.

25. The method of Claim 23, wherein the hydrochloric acid is 6 N.

26. The method of Claim 25, wherein the hydrochloric acid is added over two hours.